CRITICAL COMMENTARY 1
CENTRAL NERVOUS SYSTEM PLASTICITY AND PERSISTENT PAIN

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The idea that central sensitization following tissue injury leads to increased pain is making the transition from theoretical concept to clinical practice, as suggested in the focus article by Drs Ren and Dubner.[1] It is generally accepted that peripheral sensitization is a clinically relevant explanation for pain that follows tissue injury. The presumed role of inflammatory mediators in this process has led to the clinical practice of suppressing peripheral sensitization by administering nonsteroidal anti-inflammatory drugs (NSAIDs) prior to surgical procedures.[2,3] Recognition that the induction of cyclooxygenase-2 after injury also results in the formation of prostaglandin E_2 provides a rationale for administering NSAIDs prior to surgery to prevent pain by inhibiting the second wave of prostanoid-mediated pain. The data summarized by Ren and Dubner indicate that blocking or suppressing nociceptive input from the peripheral to the central nervous system is also important in preventing the development of central sensitization. Studies in the oral surgery model[4,5] provide evidence that the presence of acute pain during the first few hours postoperatively contributes to the development of central sensitization, such that greater pain develops at later time points up to 48 hours after the initial injury. Clinical studies that used the N-methyl-D-aspartate (NMDA) antagonist dextromethorphan for both acute[6] and chronic[7] pain also support the contribution of central sensitization to the clinical pain experience and suggest the use of drugs of this class as analgesic adjuncts. While substance P is thought to contribute to the development of central sensitization, a recent review[8] of published clinical trials provided equivocal evidence of the clinical utility of neurokinin-1 antagonists, which block the substance P receptor binding. Taken together, nociceptor activity–induced neuronal plasticity, leading to increased pain at later time points, appears to be important in the development and maintenance of clinical pain and forms the basis for therapeutic strategies that attempt to block or reverse the process.

Recognition of the role of central sensitization as a mechanism that perpetuates pain for some indeterminate period of time after the initial injury suggests several investigational approaches for temporomandibular disorders (TMD). A well-controlled trial of an NMDA antagonist, such as dextromethorphan, in comparison to placebo and positive controls would provide evidence for a contribution of central sensitization to chronic orofacial pain. A study modeled after the work of Max and colleagues in diabetic neuropathy[7,9] should include a slow titration to minimize the high incidence of side effects associated with a more rapid dose escalation[6]; a positive control that mimics somewhat the side effects normally seen with dextromethorphan; and, possibly, a crossover design to control for interindividual variation in drug metabolism, prognostic factors for chronic orofacial pain, and the many factors that influence pain report. Evaluation of the possible role of AMPA/kainate receptor–mediated events in pain chronicity awaits the availability of investigational drugs that will permit evaluation of the generalizability to clinical pain of recent observations by Sang et al for experimental pain induced by capsaicin.[10] The failure of neurokinin-1 antagonists to demonstrate activity across several models of acute and chronic pain[8] suggests that this drug class may be too selective to block the multiple nociceptive pathways that contribute to the development of central sensitization. Alternatively, once central plasticity has initiated the molecular events that lead to sensitization, blocking a prior receptor-mediated event may be no more effective than closing the proverbial barn door after the horse has escaped.

The recent introduction of drugs that block the effects of tumor necrosis factor-alpha also holds promise of the possibility of interfering with peripheral sensitization by nerve growth factor and brain-derived neurotrophic factor, as described by Ren and Dubner. The parenteral route of administration for both of these drugs may not be practical for most outpatients, but a demonstration of efficacy in an appropriately controlled clinical trial could serve to spur the development of other drugs that also act through this mechanism but are orally administered. While not mechanistically linked to central sensitization, the recently introduced COX-2 inhibitors would be predicted to block prostaglandin-mediated peripheral input, which contributes to central sensitization, and may also act as central prostanoid receptors. The hypothesis described in this focus article suggests that enhanced descending modulation mediated by serotonin may attenuate central sensitization at the spinal level, suggesting reconsideration of the use of predominantly serotonergic tricyclic antidepressants in the treatment of chronic orofacial pain.

The rich harvest of knowledge from the basic research summarized by Ren and Dubner is now leading to clinically testable hypotheses about the role of central sensitization in the development of chronic orofacial pain and novel therapeutic strategies. Given the predictive failure of hypotheses based on uncontrolled clinical observations that relate to the occlusal etiology of TMD, the need to carefully evaluate the role of central sensitization and the novel therapeutic strategies that have been suggested is obvious. Just as we now consider antibacterial treatments for periodontal disease as an alternative to traditional surgical therapy, pharmacologic therapy for chronic orofacial pain based on emerging scientific knowledge of the molecular events that contribute to plasticity in the nervous system may one day augment or replace traditional dental and surgical therapies for TMD.

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